(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 July 2006 (13.07.2006)

PCT

(10) International Publication Number
WO 2006/073292 A1

(51) International Patent Classification:
C07C 211/29 (2006.01) *A61K 31/135* (2006.01)

(21) International Application Number:
PCT/KR2006/000073

(22) International Filing Date: 6 January 2006 (06.01.2006)

(25) Filing Language: Korean

(26) Publication Language: English

(30) Priority Data:
10-2005-0001405 6 January 2005 (06.01.2005) KR

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INORGANIC ACID SALTS OF SIBUTRAMINE

(57) Abstract: Disclosed are novel inorganic acid salts of sibutramine, which have good physicochemical properties, and crystalline forms thereof . Also disclosed are pharmaceutical compositions comprising the compounds as effective ingredients, methods of preparing the compounds, and the use of the compounds.

WO 2006/073292 A1

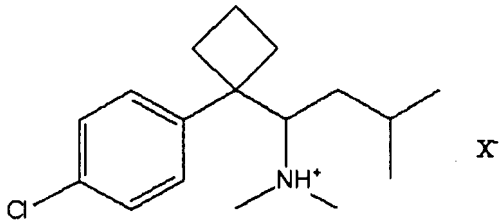
33 pgs SPEC.

INORGANIC ACID SALTS OF SIBUTRAMINE

Technical Field

The present invention relates to novel inorganic acid salts of sibutramine (N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine), represented by Chemical Formula 1, below, and crystalline forms thereof. The present invention is also concerned with pharmaceutical compositions comprising the compounds as effective ingredients, methods of preparing the compounds, and the use of the compounds.

[Chemical Formula 1]



X=HSO_4, Br, $H_2PO_4.H_2O$

Background Art

Sibutramine (N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-N,N-dimethylamine), which is a inhibitor of 5-

hydroxytryptamine and noradrenaline reuptake *in vivo* (Neuropharmacology, 28, p129-134), is useful in the treatment of depression, Parkinson's disease, obesity, insulin-independent diabetes mellitus, epilepsy, and the like. In addition, sibutramine reduces body weight gain by a dual action to reduce food intake by enhancing satiety and to increase energy expenditure by stimulating heat generation (Int. J. Obesity, 19, p145; Brit. J. Pharmacol. 114, p388).

Since sibutramine is difficult to purify due to its low melting point, it is preferable to use a crystalline material capable of being purified by recrystallization in order to prepare a pharmaceutical composition comprising sibutramine. Korean Pat. Publication No. 1990-0000274 discloses that sibutramine is utilized as salts formed with acids providing non-toxic acid addition salts containing pharmaceutically acceptable anions, for example, in the form of hydrochloride, malate, acetate, citrate, fumarate, tartrate, succinate, aspartate or glutmate salt. However, since sibutramine hydrochloride is difficult to handle pharmaceutically due to its hygroscopic nature, it is undesirable to use sibutramine hydrochloride for preparing medicaments. In the preparation of medicaments, a constant weight of an active compound should be contained in each dosage form, but an active ingredient absorbing water from the surrounding environment makes it difficult to achieve such consistency. Korean Pat. Publication No. 94-8913

discloses that when sibutramine hydrochloride is prepared in a monohydrate form, a non-hygroscopic product is obtained, which is suitable for the preparation of capsules, tablets and other pharmaceutical dosage forms.

The therapeutic use of sibutramine in depression is described in British Pat. No. 2098602. The therapeutic use of sibutramine in Parkinson's disease is disclosed in International Pat. Publication No. WO88/06444. The therapeutic use of sibutramine in cerebral function disorders is disclosed in U.S. Pat. No. 4,939,175. The use of sibutramine hydrochloride in the treatment of obesity is disclosed in European Pat. No. 397831. Also, International Pat. Publication No. WO95/20949 discloses the use of sibutramine for improving impaired glucose tolerance or glucose tolerance in patients suffering from insulin-independent diabetes mellitus.

In addition, Brazilian Pat. Publication No. 0105486 discloses a novel salt of sibutramine, sibutramine sulfate, in which two moles of sibutramine are bonded to one mole of sulfuric acid. However, this compound is structurally different from sibutramine hydrogen sulfate (in which one mole of sibutramine is bonded to one mole of sulfuric acid) according to the present invention. In particular, the Brazilian Patent Publication never mentions crystalline forms or physical properties, such as solubility and stability, of the novel salt.

Typically, the preparation of salts having pharmaceutically useful physical properties must satisfy the following physicochemical criteria: (1) good solubility, (2) good stability, (3) good non-hygroscopicity and (4) compressibility into tablet form.

However, Korean Pat. Publication No. 94-8913 states that sibutramine hydrochloride has been known to contain a variable amount of water and thus be hygroscopic, and that non-hygroscopic sibutramine can be obtained by preparing sibutramine hydrochloride in a monohydrate form. Sibutramine hydrochloride monohydrate has been prepared by brining it into contact with a medium consisting of water or a medium containing water.

Thus, sibutramine hydrochloride monohydrate is prepared by a complicated process including adding a predetermined amount of water to a reaction mixture, or including preparing sibutramine hydrochloride anhydrate and suspending the sibutramine hydrochloride anhydrate in a water-containing solvent for a long time with agitation. In addition, since currently available sibutramine hydrochloride monohydrate has relatively low solubility between pH 1.0 and pH 7.4, substitute salts having better solubility need to be developed in order to improve the bioavailability of sibutramine. The term "sibutramine", as used herein, refers to racemic sibutramine, unless otherwise indicated.

Based on this background, the present inventors found

that hydrogen sulfate and bromate salts of sibutramine possess remarkably high solubility in water as well as having non-hygroscopicity and stability, and that sibutramine phosphate hydrate has greatly enhanced solubility even when it exists in a hydrous form, compared to conventional sibutramine hydrochloride hydrate, thereby leading to the present invention.

Disclosure of the Invention

In this regard, intensive and through research into the development of a novel salt of sibutramine, capable of solving the problems encountered in the prior art, conducted by the present inventors, resulted in the finding that inorganic acid salts of sibutramine, particularly hydrogen sulfate, bromate, and phosphate monohydrate, possess good physicochemical properties (solubility, non-hygroscopicity and stability). The present inventors further found that sibutramine anhydrate can be prepared with no additional complicated procedure of adding a predetermined amount of water in order to prepare a hydrous form of sibutramine, and has remarkably high solubility although it is in an anhydrous form, as well as being non-hygroscopic, and that the inorganic acids used are less-toxic acids that have been used in many medicaments, thereby leading to the present invention.

It is therefore an object of the present invention to provide a pharmaceutical composition for treating and preventing pathological states of obesity and related disorders, comprising an inorganic acid salt of sibutramine, which has increased water solubility, is non-hygroscopic, and is stable to heat, as an active ingredient.

It is another object of the present invention to provide the inorganic acid salt of sibutramine, and a method of preparing the same.

It is a further object of the present invention to provide anhydrous crystalline and hydrous crystalline forms of the inorganic acid salt of sibutramine.

It is yet another object of the present invention to provide a pharmaceutical composition comprising the inorganic acid salt of sibutramine as an effective ingredient along with a pharmaceutically acceptable diluent or carrier.

It is still another object of the present invention to provide a method of treating obesity, depression, Parkinson's disease, insulin-independent diabetes mellitus and epilepsy using the inorganic acid salt of sibutramine as an effective ingredient.

Brief Description of the Drawings

The above and other objects, features and other

advantages of the present invention will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

Fig. 1 is an X-ray diffraction spectrum of a first crystalline sibutramine hydrogen sulfate according to Example 1;

Fig. 2 is an X-ray diffraction spectrum of a first crystalline sibutramine hydrogen sulfate according to Example 2;

Fig. 3 is an X-ray diffraction spectrum of a first crystalline sibutramine hydrogen sulfate according to Example 3;

Fig. 4 is an X-ray diffraction spectrum of a first crystalline sibutramine hydrogen sulfate according to Example 4;

Fig. 5 is an X-ray diffraction spectrum of a first crystalline sibutramine hydrogen sulfate according to Example 5;

Fig. 6 is an X-ray diffraction spectrum of a first crystalline sibutramine hydrogen sulfate according to Example 6;

Fig. 7 is an X-ray diffraction spectrum of a second crystalline sibutramine hydrogen sulfate according to Example 7;

Fig. 8 is an X-ray diffraction spectrum of a third crystalline sibutramine hydrogen sulfate according to Example

8;

Fig. 9 is an X-ray diffraction spectrum of crystalline sibutramine bromate according to Example 9; and

Fig. 10 is an X-ray diffraction spectrum of crystalline sibutramine phosphate hydrate according to Example 10.

Best Mode for Carrying Out the Invention

To accomplish the objects of the present invention, the present invention provides inorganic acid salts of sibutramine, preferably crystalline sibutramine hydrogen sulfate and crystalline sibutramine bromate in anhydrous forms, and crystalline sibutramine phosphate monohydrate in a hydrous form.

The present invention also provides a method of preparing an inorganic acid salt of sibutramine, comprising reacting sibutramine with an inorganic acid selected from among sulfuric acid, bromic acid, and phosphoric acid in an inert solvent.

The present invention further provides methods of preparing anhydrous crystalline and hydrous crystalline forms of an inorganic acid salt of sibutramine.

The present invention still further provides a pharmaceutical composition for treating obesity, comprising a therapeutically effective amount of an inorganic acid salt

of sibutramine and a pharmaceutically acceptable diluent or carrier. The present invention provides a method of treating obesity, comprising administering the therapeutically effective amount of the inorganic acid salt of sibutramine.

The present invention still further provides a pharmaceutical composition for treating depression, comprising a therapeutically effective amount of an inorganic acid salt of sibutramine and a pharmaceutically acceptable diluent or carrier. The present invention provides a method of treating depression, comprising administering the therapeutically effective amount of the inorganic acid salt of sibutramine.

The present invention still further provides a pharmaceutical composition for treating Parkinson's disease, comprising a therapeutically effective amount of an inorganic acid salt of sibutramine and a pharmaceutically acceptable diluent or carrier. The present invention provides a method of treating Parkinson's disease, comprising administering the therapeutically effective amount of the inorganic acid salt of sibutramine.

The present invention still further provides a pharmaceutical composition for treating insulin-independent diabetes mellitus, comprising a therapeutically effective amount of an inorganic acid salt of sibutramine and a pharmaceutically acceptable diluent or carrier. The present

invention provides a method of treating insulin-independent diabetes mellitus, comprising administering the therapeutically effective amount of the inorganic acid salt of sibutramine.

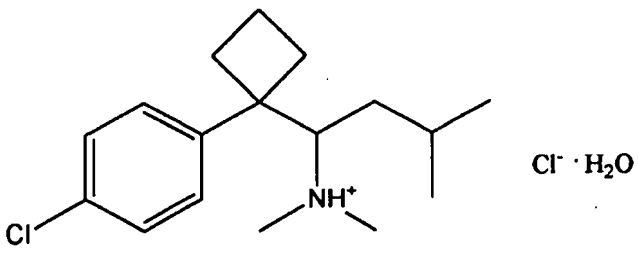
The present invention still further provides a pharmaceutical composition for treating epilepsy, comprising a therapeutically effective amount of an inorganic acid salt of sibutramine and a pharmaceutically acceptable diluent or carrier. The present invention provides a method of treating epilepsy, comprising administering the therapeutically effective amount of the inorganic acid salt of sibutramine.

The pharmaceutical composition of the present invention is preferably formulated into tablets or capsules.

Hereinafter, the present invention will be described in more detail.

The present invention relates to an inorganic acid salt of sibutramine, represented by Chemical Formula 1.

[Chemical Formula 2]



Sibutramine bromate anhydrate according to the present invention displays solubility, non-hygroscopicity, formulability and chemical stability, identical to or better than the commercially available sibutramine hydrochloride monohydrate of Chemical Formula 2. Sibutramine hydrogen sulfate and sibutramine phosphate hydrate exhibit non-hygroscopicity, formulability chemical stability and flowability, identical to or better than sibutramine hydrochloride monohydrate, and in particular exhibit about at least 10 times greater solubility in distilled water and buffer solutions of pH 1.2, pH 4.0, pH 5.3, pH 6.8 and pH 7.4. With respect to non-hygroscopicity, the aforementioned inorganic acid salts of sibutramine display no hygroscopicity and no decrease in water content when they are exposed to relative humidities of 10%, 75% and 90% for a period of seven days or longer. With respect to stability, the inorganic acid salts of sibutramine do not generate impurities and do not change in content even when they are exposed to a high temperature of 60℃ for a period of one month or longer. The inorganic acid salts of sibutramine also exhibit good photostability.

The present inventors learned about that the sulfuric, phosphoric and bromic acids, contained in the inorganic acid salts of sibutramine according to the present invention, are typically used in a number of medicaments and are less-toxic acids that have been proven

safe for long-term use, and concluded that the novel inorganic acid salts of sibutramine are suitable for long-term administration, thereby leading to the present invention.

The inorganic acid salts of sibutramine according to the present invention may be crystalline or non-crystalline. Crystalline forms of the inorganic acid salts of sibutramine are preferred with respect to physical properties such as non-hygroscopicity and thermodynamical stability.

The present invention includes a method of preparing the inorganic acid salt of sibutramine. That is, the present invention includes a method of preparing an inorganic acid salt of sibutramine, comprising reacting sibutramine with an inorganic acid in an inert solvent. The reaction using sulfuric acid among inorganic acids used takes place according to the following Reaction 1.

[Reaction 1]

Among the inorganic acids used as reactants, sulfuric acid has a reported oral-rat LD_{50} of 2,140 mg/kg, and has

been used in a number of medicaments, including clopidogrel, cefpirome, amphetamine, salbutamol and gentamycin.

In an embodiment, a first crystalline sibutramine hydrogen sulfate is prepared using acetone, ethyl acetate, ethanol, acetonitrile, methylethyl ketone or methylene chloride as an inert solvent according to the method. This compound is characterized by having an X-ray diffraction pattern in which peaks ($I/I_0 \geq 200$) appear at 2θ values of 6.50, 12.18, 12.38, 12.58, 13.06, 14.00, 16.76, 17.04, 18.06, 19.68, 20.32, 20.63, 21.34, 21.82, 22.28, 22.54, 23.32, 24.50, 25.80, 26.42, 28.24, 28.64, 29.28, and 33.34.

In another embodiment, a second crystalline sibutramine hydrogen sulfate is prepared using isopropylether as an inert solvent according to the method. This compound is characterized by having an X-ray diffraction pattern in which peaks ($I/I_0 \geq 100$) appear at 2θ values of 5.73, 6.49, 12.18, 12.51, 13.13, 14.02, 14.79, 16.97, 17.38, 20.62, 21.40, 21.83, 22.31, 22.68, 24.51, 24.88, 25.82, 26.45, and 31.60.

In a further embodiment, a third crystalline sibutramine hydrogen sulfate is prepared using methanol and isopropylether as an inert solvent mixture according to the method. This compound is characterized by having an X-ray diffraction pattern in which peaks ($I/I_0 \geq 100$) appear at 2θ values of 6.64, 10.24, 13.03, 15.04, 17.00, 17.53, 17.08,

19.06, 20.52, 22.72, 23.23, 24.23, 25.70, 26.40, and 27.57.

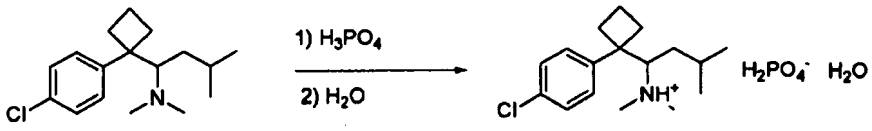
The reaction using bromic acid among inorganic acids used takes place according to the following Reaction 2.

[Reaction 2]

The bromic acid used as a reactant has a reported oral-mouse LD_{50} of 2,700 mg/kg, and has been used in a number of medicaments, including citalopram, dextromethorphan, fenoterol, galantamine and scopolamine. In detail, the product of Reaction 2, crystalline sibutramine bromate, is characterized by having an X-ray diffraction pattern in which peaks ($I/I_0 \geq 200$) appear at 2θ values of 6.96, 11.48, 13.88, 16.64, 17.14, 18.14, 19.68, 20.92, 21.32, 21.86, 22.16, 22.86, 24.30, 26.16, 26.40, 27.42, 28.06, 28.32, 29.52, 31.58, 32.94, 34.54, 37.42, and 37.82.

The reaction using phosphoric acid among inorganic acids used takes place according to the following Reaction 3.

[Reaction 3]



The phosphoric acid used as a reactant has a reported oral-rat LD_{50} of 1,530 mg/kg, and has been used in a number of medicaments, including clindamycin, chloroquine, codeine, disopyramide, metromidazole and oleandomycin. In detail, the product of Reaction 3, crystalline sibutramine phosphate, is characterized by having an X-ray diffraction pattern in which peaks ($I/I_0 \geq 200$) appear at 2θ values of 7.66, 10.68, 11.06, 11.50, 14.46, 15.40, 15.74, 17.22, 17.84, 18.08, 18.98, 19.68, 21.18, 21.50, 21.88, 22.84, 23.18, 23.62, 24.42, 24.72, 25.98, 27.52, 28.38, 28.64, and 29.28.

The inorganic acids used in Reactions 1, 2 and 3 are are less-toxic acids that haven been proven safe for long-term use.

The inert solvent available in the preparation method of the present invention includes acetone, ethyl acetate, methanol, ethanol, isopropanol, acetonitrile, isopropyl ether, methylethyl ketone and dichloromethane. Acetone and ethyl acetate are preferred.

In the inert solvent, one equivalent of sibutramine may be reacted with 1 to 2 equivalents, preferably 1.02 to 1.2 equivalents, of concentrated sulfuric acid, at -5 to 40℃, preferably 20 to 30℃, for 0.5 to 5 hours, preferably

2 to 3 hours. Herein, the concentrated sulfuric acid is used after being diluted with the inert solvent.

The preparation method of the present invention may provide an inorganic acid salt of sibutramine in a yield of higher than 90.0% and a high purity of greater than 99.0%.

The present invention provides a pharmaceutical composition for treating or preventing pathological states of obesity and related disorders, comprising a therapeutically effective amount of hydrogen sulfate, bromate or phosphate monohydrate of sibutramine and a pharmaceutically acceptable diluent or carrier, and a method of treating or preventing pathological states of obesity and related disorders by administering this composition.

The present invention also provides a pharmaceutical composition for treating depression, comprising a therapeutically effective amount of an inorganic acid salt of sibutramine and a pharmaceutically acceptable diluent or carrier, and a method of treating depression by administering this composition.

The present invention further provides a pharmaceutical composition for treating or preventing Parkinson's disease, comprising a therapeutically effective amount of an inorganic acid salt of sibutramine and a pharmaceutically acceptable diluent or carrier, and a method of treating or preventing Parkinson's disease by

administering this composition.

The present invention still further provides a pharmaceutical composition for treating insulin-independent diabetes mellitus, comprising a therapeutically effective amount of an inorganic acid salt of sibutramine and a pharmaceutically acceptable diluent or carrier, and a method of treating insulin-independent diabetes mellitus by administering this composition.

The present invention still further provides a pharmaceutical composition for treating epilepsy, comprising a therapeutically effective amount of an inorganic acid salt of sibutramine and a pharmaceutically acceptable diluent or carrier, and a method of treating epilepsy by administering this composition.

The pharmaceutical composition comprising the inorganic acid salt of sibutramine according to the present invention as an active ingredient may be preferably administered orally, for example in the form of tablets or capsules.

Tablets may be prepared by mixing an active ingredient with a carrier, a diluent or an excipient and compressing the mixture into tablets. Examples of suitable carriers, diluents or excipients include disintegrators such as starch, sugars and mannitol; fillers and extenders such as calcium phosphate and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose

derivatives, gelatin and polyvinyl pyrrolidone; and lubricants such as talc, calcium and magnesium stearate, and solid polyethylene glycol. Also, hard or soft gelatin capsules containing an active ingredient, either with or without an additive such as the carriers, diluents or excipients may be prepared according to an ordinary method.

The pharmaceutical composition preferably contains a crystalline inorganic acid salt of sibutramine, represented by Chemical Formula 1, as an active ingredient in an amount of 1 to 50 parts by weight based on 250 parts by weight of the composition.

For example, the pharmaceutical composition having a total weight of 250 mg according to the present invention may be prepared in such a manner as to contain 10 mg (based on sibutramine content) of the crystalline inorganic acid salt of sibutramine, represented by Chemical Formula 1, 115 mg of microcrystalline cellulose, 115 mg of lactose, 5 mg of silicon dioxide, and 5 mg of magnesium stearate. However, this composition of the pharmaceutical composition is illustrative, and thus, the scope of the present invention is not limited thereto.

A better understanding of the present invention may be obtained through the following examples which are set forth to illustrate, but are not to be construed as the limit of the present invention.

REFERENCE EXAMPLE 1: Preparation of sibutramine hydrochloride monohydrate

Sibutramine hydrochloride anhydrate was prepared according to a method described in Korean Pat. No. 2098602 or Korean Pat. Publication No. 90-00274. Then, according to a method described in British Pat. No. 2184122 or Korean Pat. Publication No. 94-08913, 10 g of the prepared sibutramine hydrochloride anhydrate was dissolved in a boiling mixture of 110 ml acetone and 1.2 ml water, and the resulting solution was hot-filtered and distilled to remove 80 ml of the solvent, thus reducing the volume of the filtrate. The concentrate was filtered to recover a generated solid. The solid was vacuum-dried, thus obtaining 9.2 g (yield: 87%) of the compound of Chemical Formula 2, which had a melting point of 195℃.

EXAMPLES

Hydrogen sulfate, bromate and phosphate monohydrate salts of sibutramine were prepared according to the preparation method of the present invention, and were compared with sibutramine hydrochloride hydrate for physical properties including hygroscopicity, solubility, stability, light stability and crystallizability. In addition, the inorganic acid salts of sibutramine were

formulated into capsules in order to examine their formulability and release patterns.

EXAMPLE 1: Preparation of sibutramine hydrogen sulfate using acetone

Sibutramine (17.1 g, 0.06 mol) was dissolved in 150 ml of acetone with agitation. After the solution was adjusted to 25℃, 6.0 g of concentrated sulfuric acid was diluted with 50 ml of acetone and added to the solution. Crystals formed slowly. The resulting mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 30 ml of acetone, and vacuum-dried at 40℃, thus obtaining 21.0 g (yield: 91%) of a target compound.

TABLE 1

Elemental analysis ($C_{17}H_{28}ClNO_4S$)	Unit (%)
Measured value	C: 54.35, H: 7.68, N: 3.82, O: 17.00, S: 8.58
Theoretical value	C: 54.03, H: 7.47, N: 3.71, O: 16.93, S: 8.4

Melting point (DSC): 212.8℃

^{1}H-NMR (δ, DMSO-d6): 8.39 (1H, br, s), 7.54~7.49 (4H, dd), 3.75 (1H, t), 2.83 (3H, d), 2.5 (2H, d), 2.33 (2H, t), 2.13 (3H, d), 1.90 (1H, m), 1.70~1.67 (2H, m), 1.40 (2H, m), 1.00 (6H, t)

EXAMPLE 2: Preparation of sibutramine hydrogen sulfate using ethyl acetate

Sibutramine (17.1 g, 0.06 mol) was dissolved in 150 ml of ethyl acetate with agitation. After the solution was adjusted to 25℃, 6.0 g of concentrated sulfuric acid was diluted with 50 ml of ethyl acetone and added to the solution. Crystals formed slowly. The resulting mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 50 ml of ethyl acetate, and vacuum-dried at 40℃, thus obtaining 21.5 g (yield: 94%) of a target compound.

Melting point: 212℃

EXAMPLE 3: Preparation of sibutramine hydrogen chloride using ethanol

Sibutramine (17.1 g, 0.06 mol) was dissolved in 70 ml of ethanol with agitation. After the solution was adjusted to 25℃, 6.0 g of concentrated sulfuric acid was diluted with 10 ml of ethanol and added to the solution to slowly form crystals. The resulting mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 50 ml of acetone, and vacuum-dried at 40℃, thus

obtaining 20.3 g (yield: 89.5%) of a target compound.

Melting point: 211℃

EXAMPLE 4: Preparation of sibutramine hydrogen chloride using acetonitrile

Sibutramine (17.1 g, 0.06 mol) was dissolved in 150 ml of acetonitrile with agitation. After the solution was adjusted to 25℃, 6.0 g of concentrated sulfuric acid was diluted with 50 ml of acetonitrile and added to the solution. Crystals formed slowly. The resulting mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 50 ml of acetonitrile, and vacuum-dried at 40℃, thus obtaining 21.0 g (yield: 92%) of a target compound.

Melting point: 211℃

EXAMPLE 5: Preparation of sibutramine hydrogen sulfate using methylethyl ketone

Sibutramine (17.1 g, 0.06 mol) was dissolved in 150 ml of methylethyl ketone with agitation. After the solution was adjusted to 25℃, 6.0 g of concentrated sulfuric acid was diluted with 50 ml of methylethyl ketone and added to the solution. Crystals formed slowly. The resulting

mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 50 ml of methylethyl ketone, and vacuum-dried at 40℃, thus obtaining 22.0 g (yield: 97%) of a target compound.

Melting point: 212℃

EXAMPLE 6: Preparation of sibutramine hydrogen sulfate using methylene chloride

Sibutramine (17.1 g, 0.06 mol) was dissolved in 150 ml of methylene chloride with agitation. After the solution was adjusted to 25℃, 6.0 g of concentrated sulfuric acid was diluted with 50 ml of methylene chloride and added to the solution. Crystals formed slowly. The resulting mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 50 ml of methylene chloride, and vacuum-dried at 40℃, thus obtaining 20.3 g (yield: 90%) of a target compound.

Melting point: 211℃

EXAMPLE 7: Preparation of sibutramine hydrogen sulfate using isopropyl ether

Sibutramine (17.1 g, 0.06 mol) was dissolved in 150

ml of isopropyl ether with agitation. After the solution was adjusted to 25℃, 6.0 g of concentrated sulfuric acid was diluted with 50 ml of isopropyl ether and added to the solution. Crystals formed immediately after isopropyl ether addition. The resulting mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 50 ml of isopropyl ether, and vacuum-dried at 40℃, thus obtaining 22.1 g (yield: 97%) of a target compound.

Melting point: 207℃

EXAMPLE 8: Preparation of sibutramine hydrogen sulfate using methanol and isopropyl ether

Sibutramine (17.1 g, 0.06 mol) was dissolved in 50 ml of methanol with agitation. After the solution was adjusted to 25℃, 6.0 g of concentrated sulfuric acid was diluted with 10 ml of methanol and added to the solution. The reaction solution was concentrated from 30 ml to 15 ml under pressure. 150 ml of isopropyl ether was slowly added in droplets to the concentrate for 10 min. The resulting mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 50 ml of isopropyl ether, and vacuum-dried at 40℃, thus obtaining 20.3 g (yield: 90%) of a target compound.

Melting point: 210℃

EXAMPLE 9: Preparation of sibutramine bromate

Sibutramine (28.0 g, 0.1 mol) was dissolved in 280 ml of ethyl acetate with agitation. After the solution was adjusted to 25℃, 17.2 g of 47% bromic acid was slowly added in droplets to the solution to form crystals. The resulting mixture was agitated at 25℃ for 2 hrs and further agitated at 4℃ for 1 hr. The generated solid was recovered by filtration under pressure, washed with 100 ml of ethyl acetate, and vacuum-dried at 40℃, thus obtaining 33.1 g (yield: 92%) of a target compound.

TABLE 2

Elemental analysis ($C_{17}H_{27}BrClN$)	Unit (%)
Measured value	C: 56.79, H: 7.77, N: 3.89
Theoretical value	C: 56.60, H: 7.54, N: 3.88

Melting point (DSC): 212.4℃

^{1}H-NMR (δ, DMSO-d6): 8.61 (1H, br, s), 7.60~7.48 (4H, dd), 3.80 (1H, t), 2.83 (3H, d), 2.50 (2H, d), 2.32 (2H, t), 2.20 (3H, d), 1.90 (1H, m), 1.77~1.68 (2H, m), 1.39 (2H, m), 1.00(6H, t)

EXAMPLE 10: Preparation of sibutramine phosphate monohydrate

10 g of sibutramine was dissolved in 100 ml of ethyl acetate with agitation. After the solution was adjusted to 25℃, 4.13 g of 85% phosphoric acid was diluted with 30 ml of ethyl acetate and added in droplets to the solution. Crystals formed slowly. The resulting mixture was agitated at 25℃ for 2 hrs. The generated solid was recovered by filtration under pressure and washed with 30 ml of ethyl acetate. The washed sibutramine phosphate anhydrate was mixed with 120 ml of isopropyl ether, 50 ml of acetone and 1.5 ml of water, agitated at 20-30℃ for 18 hrs, filtered, and vacuum-dried, thus obtaining 12.8 g (yield: 90%) of a target compound.

The obtained sibutramine phosphate monohydrate was subjected to elemental analysis and melting point analysis, and the results are as follows.

TABLE 3

Elemental analysis ($C_{17}H_{31}ClNO_5P$)	Unit (%)
Measured value	C: 51.38, H: 7.69, N: 3.50, O: 19.62
Theoretical value	C: 51.58, H: 7.89, N: 3.54, O: 20.21

Melting point (DSC): 174.1℃

^{1}H-NMR (δ, DMSO-d6): 8.14 (1H, br, s), 7.38~7.30 (4H, dd), 3.14 (1H, t), 2.51 (1H, d), 2.45 (1H, d), 2.33 (1H, m), 2.22 (5H, t), 2.18 (3H, t), 1.90 (1H, m), 1.67 (1H, m), 1.56 (1H, m), 1.19 (2H, m), 0.95 (3H, d), 0.89 (3H, d)

EXAMPLE 11: Preparation of capsules containing sibutramine hydrogen sulfate

Ingredients were mixed according to the composition described in Table 4, below, to prepare capsules containing sibutramine hydrogen sulfate.

TABLE 4

Ingredients	Content (per capsule)
Sibutramine hydrogen sulfate	Amount corresponding to 10 mg of sibutramine
Lactose	115 mg
Microcrystalline cellulose	115 mg
Silicon dioxide	5 mg
Magnesium stearate	5 mg

The ingredients were mixed and filled into hard capsules using a capsule filling machine (Bosche).

EXAMPLE 12: Preparation of capsules containing sibutramine bromate

Ingredients were mixed according to the composition described in Table 5, below, to prepare capsules containing sibutramine bromate.

TABLE 5

Ingredients	Content (per capsule)
Sibutramine bromate	Amount corresponding to 10 mg of sibutramine

Lactose	115 mg
Microcrystalline cellulose	115 mg
Silicon dioxide	5 mg
Magnesium stearate	5 mg

The ingredients were mixed and filled into hard capsules using a capsule filling machine (Bosche).

EXAMPLE 13: Preparation of capsules containing sibutramine phosphate monohydrate

Ingredients were mixed according to the composition described in Table 6, below, to prepare capsules containing sibutramine phosphate monohydrate.

TABLE 6

Ingredients	Content (per capsule)
Sibutramine phosphate monohydrate	Amount corresponding to 10 mg of sibutramine
Lactose	115 mg
Microcrystalline cellulose	115 mg
Silicon dioxide	5 mg
Magnesium stearate	5 mg

The ingredients were mixed and filled into hard capsules using a capsule filling machine (Bosche).

EXAMPLE 14: Evaluation of hygroscopicity of the inorganic acid salts of sibutramine

The inorganic acid salts of sibutramine, prepared in

Examples 1, 2 and 3, and sibutramine hydrochloride monohydrate were exposed to humid conditions (75% and 90% RH) at 25℃ for a period of three days or one weeks. Then, the water content (K.F. water%) of the samples was measured. The results are given in Table 7, below.

TABLE 7

Storage humidity (relative humidity)		75%		90%	
Storage period	Initial	3 days		1 week	
Sibutramine hydrogen sulfate	0.02%	0.02%	0.01%	0.03%	0.03%
sibutramine bromate	0.09%	0.09%	0.09%	0.08%	0.08%
Sibutramine phosphate hydrate	4.25%	4.24%	4.25%	4.25%	4.26%
Sibutramine HCl hydrate	5.5%	5.49%	5.5%	5.5%	5.49%

As shown in Table 7, like sibutramine hydrochloride hydrate, hydrogen sulfate, bromate and phosphate hydrate salts of sibutramine displayed almost no change in water content under humid conditions.

EXAMPLE 15: Evaluation of solubility of the inorganic acid salts of sibutramine

The inorganic acid salts of sibutramine, prepared in Examples 1, 2 and 3, and sibutramine hydrochloride monohydrate were evaluated for solubility in solutions having various pH values. The results are given in Table 8, below. In Table 8, the solubility is expressed as milligrams (mg) of sibutramine dissolved per milliliter (ml) of solution.

TABLE 8

Solvents	Salts of sibutramine				Remarks
	Hydrogen sulfate	Bromate	Phosphate	Hydrochloride	
DW	285	12.78	38.86	26.18	Dissolved at 37℃
pH 1.2	333	12.43	23.92	13.36	
pH 4.0	333	3.64	50	9.58	
pH 5.3	400	8.96	50	6.58	
pH 6.8	370	11.08	24.55	23.14	
pH 7.4	400	12.41	50	9.2	

As shown in Table 8, in distilled water (DW) and buffer solutions at various pH values, hydrogen sulfate and phosphate salts of sibutramine had greatly enhanced solubility compared to sibutramine hydrochloride. These results indicate that these salt forms of sibutramine may have better bioavailability than sibutramine hydrochloride monohydrate.

EXAMPLE 16: Evaluation of stability of the inorganic acid salts of sibutramine

The inorganic acid salts of sibutramine, prepared in Examples 1, 2 and 3, and sibutramine hydrochloride monohydrate were exposed to a stringent 60℃ heat treatment. The results are summarized in Table 9, below.

TABLE 9

Storage period	Initial	1 wk	2 wks	4 wks
Hydrogen sulfate	1.000	1.000	0.999	0.999

Bromate	1.000	0.999	1.000	0.999
Phosphate	1.000	1.000	0.999	1.000
Hydrochloride	1.000	1.000	0.999	0.999

HPLC was performed under the following conditions.

Wavelength of UV detection: 225 nm

Column: octadecyl silica gel, C18 (4.6×150 mm, 5 ㎛)

Mobile phase: ammonium phosphate monohydride (0.05 M, adjusted to pH 6.0 with phosphoric acid) : acetonitrile = 35 : 65

Flow rate: 1.0 ml/min

As shown in Table 9, like sibutramine hydrochloride monohydrate, the inorganic acid salts of sibutramine displayed almost no change in content upon stringent 60℃ heat treatment. These results indicate that the hydrogen sulfate, bromate and phosphate monohydrate salts of sibutramine, like sibutramine hydrochloride monohydrate, have good chemical stability at high temperature.

EXAMPLE 17: valuation of light stability of the inorganic acid salts of sibutramine

A light stability test was performed as follows. The inorganic acid salts of sibutramine, prepared in Examples 1, 2 and 3, and sibutramine hydrochloride monohydrate were exposed to fluorescent light at 25℃ using a light stability test chamber suitable for the ICH guideline, for storage

periods of 1, 2 and 4 weeks. The results are given in Table 10, below.

TABLE 10

Storage period	Initial	1 wk	2 wks	4 wks
Hydrogen sulfate	1.000	1.000	1.000	0.999
Bromate	1.000	1.000	0.999	0.999
Phosphate monohydrate	1.000	1.000	0.999	0.999
HCl monohydrate	1.000	1.000	0.999	0.999

As shown in Table 10, when content changes of the inorganic acid salts of sibutramine were analyzed by HPLC in order to determine their light stability, the inorganic acid salts of sibutramine, like sibutramine hydrochloride monohydrate, displayed good light stability.

Industrial Applicability

The hydrogen sulfate, bromate and phosphate monohydrate salts of sibutramine according to the present invention have good physicochemical properties including non-hygroscopicity, solubility, stability, formulability and crystallizability. The hydrogen sulfate and phosphate monohydrate salts of sibutramine exhibit an increased solubility, more than 10 times that of sibutramine hydrochloride hydrate. In addition, due to their non-hygroscopic nature, since the hydrogen sulfate, bromate and phosphate monohydrate salts of sibutramine do not change in

content, they are highly suitable for long-term storage and guarantee consistency suitable for the preparation of pharmaceutical dosage forms.

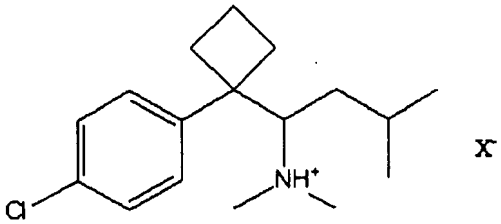
Moreover, since sulfuric, bromic and phosphoric acids used in the preparation of the novel inorganic acid salts of sibutramine are less-toxic acids that haven been proven to be pharmaceutically safe for long-term use, the inorganic acid salts of sibutramine are useful as novel salts of sibutramine.

4 pgs clms

Claims

1. An inorganic acid salt of sibutramine, which has a structure of Chemical Formula 1, below, the inorganic acid salt being hydrogen sulfate, bromate or phosphate monohydrate.

[Chemical Formula 1]



$X = HSO_4$, Br, $H_2PO_4 \cdot H_2O$

2. The inorganic acid salt of sibutramine as set forth in claim 1, wherein the sibutramine hydrogen sulfate is a first crystalline sibutramine hydrogen sulfate having an X-ray diffraction pattern in which peaks appear at 2θ values of 6.50, 12.18, 12.38, 12.58, 13.06, 14.00, 16.76, 17.04, 18.06, 19.68, 20.32, 20.63, 21.34, 21.82, 22.28, 22.54, 23.32, 24.50, 25.80, 26.42, 28.24, 28.64, 29.28, and 33.34.

3. The inorganic acid salt of sibutramine as set

forth in claim 1, wherein the sibutramine hydrogen sulfate is a second crystalline sibutramine hydrogen sulfate having an X-ray diffraction pattern in which peaks appear at 2θ values of 5.73, 6.49, 12.18, 12.51, 13.13, 14.02, 14.79, 16.97, 17.38, 20.62, 21.40, 21.83, 22.31, 22.68, 24.51, 24.88, 25.82, 26.45, and 31.60.

4. The inorganic acid salt of sibutramine as set forth in claim 1, wherein the sibutramine hydrogen sulfate is a third crystalline sibutramine hydrogen sulfate having an X-ray diffraction pattern in which peaks appear at 2θ values of 6.64, 10.24, 13.03, 15.04, 17.00, 17.53, 17.08, 19.06, 20.52, 22.72, 23.23, 24.23, 25.70, 26.40, and 27.57.

5. The inorganic acid salt of sibutramine as set forth in claim 1, wherein the sibutramine bromate is crystalline sibutramine bromate having an X-ray diffraction pattern in which peaks appear at 2θ values of 6.96, 11.48, 13.88, 16.64, 17.14, 18.14, 19.68, 20.92, 21.32, 21.86, 22.16, 22.86, 24.30, 26.16, 26.40, 27.42, 28.06, 28.32, 29.52, 31.58, 32.94, 34.54, 37.42, and 37.82.

6. The inorganic acid salt of sibutramine as set forth in claim 1, wherein the sibutramine phosphate monohydrate is crystalline sibutramine phosphate monohydrate having an X-ray diffraction pattern in which

peaks appear at 2θ values of 7.66, 10.68, 11.06, 11.50, 14.46, 15.40, 15.74, 17.22, 17.84, 18.08, 18.98, 19.68, 21.18, 21.50, 21.88, 22.84, 23.18, 23.62, 24.42, 24.72, 25.98, 27.52, 28.38, 28.64, and 29.28.

7. A method of preparing the sibutramine hydrogen sulfate according to claim 1, comprising reacting sibutramine and sulfuric acid.

8. A method of preparing the sibutramine bromate according to claim 1, comprising reacting sibutramine and bromic acid.

9. A method of preparing the sibutramine phosphate and phosphate monohydrate according to claim 1, comprising reacting sibutramine and phosphoric acid.

10. The method as set forth in any one of claims 7 to 9, wherein the reaction takes place in an organic solvent selected from the group consisting of acetone, ethyl acetate, methanol, ethanol, isopropanol, acetonitrile, isopropyl ether, methylethyl ketone, dichloromethane and combination thereof.

11. A pharmaceutical composition for treating or preventing obesity and related disorders, depression,

Parkinson's disease, insulin-independent diabetes mellitus or epilepsy, comprising a therapeutically effective amount of the sibutramine hydrogen sulfate, sibutramine bromate or sibutramine phosphate monohydrate according to claim 1 and a pharmaceutically acceptable diluent or carrier.

12. The pharmaceutical composition as set forth in claim 11, wherein the sibutramine hydrogen sulfate, sibutramine bromate or sibutramine phosphate is contained in a therapeutically effective amount of 1 to 50 mg.

13. A method of treating or preventing obesity and related disorders, depression, Parkinson's disease, insulin-independent diabetes mellitus or epilepsy, comprising administering the pharmaceutical composition of claim 11.

10 pgs - DRWS

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Fig. 1

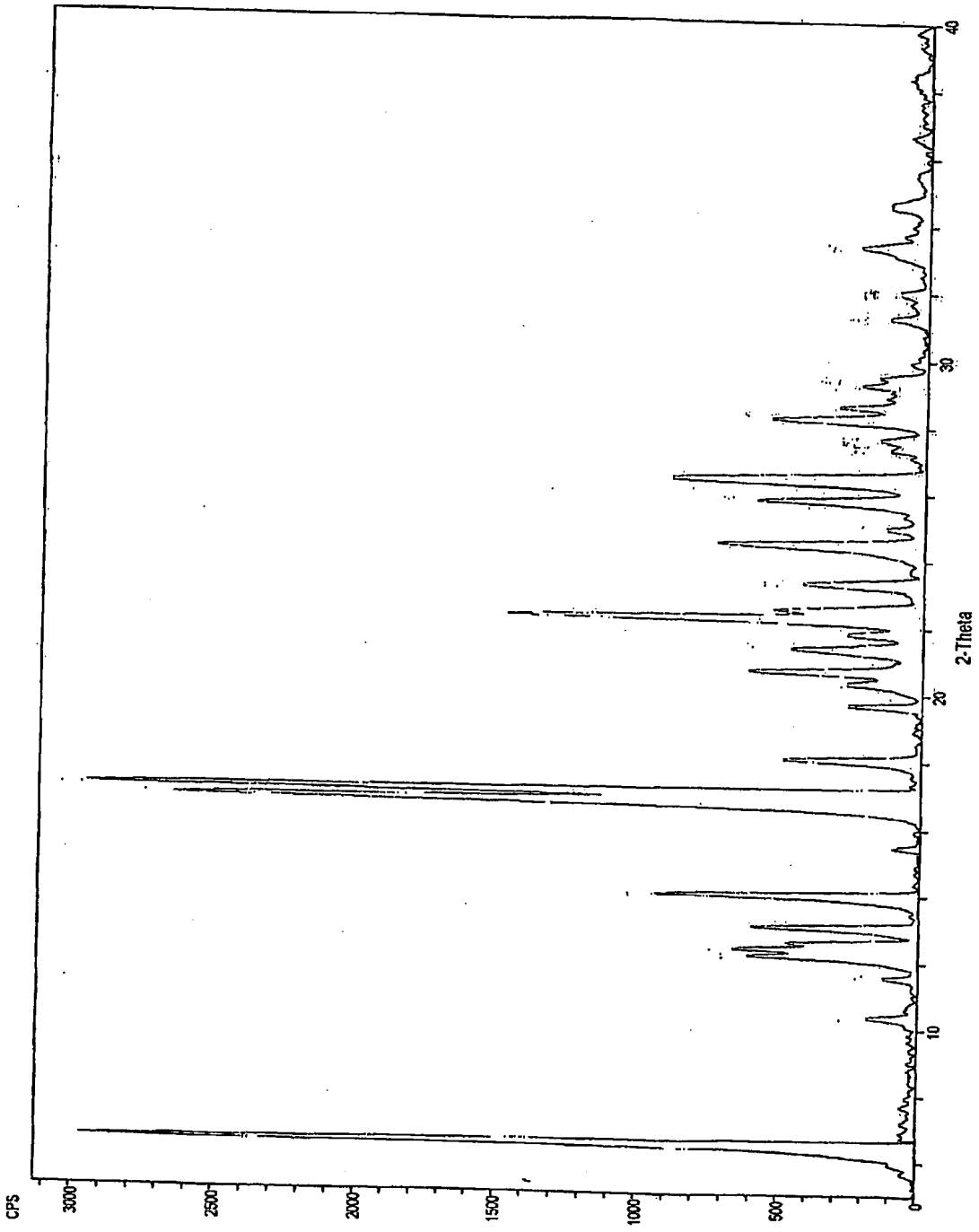

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Fig. 2

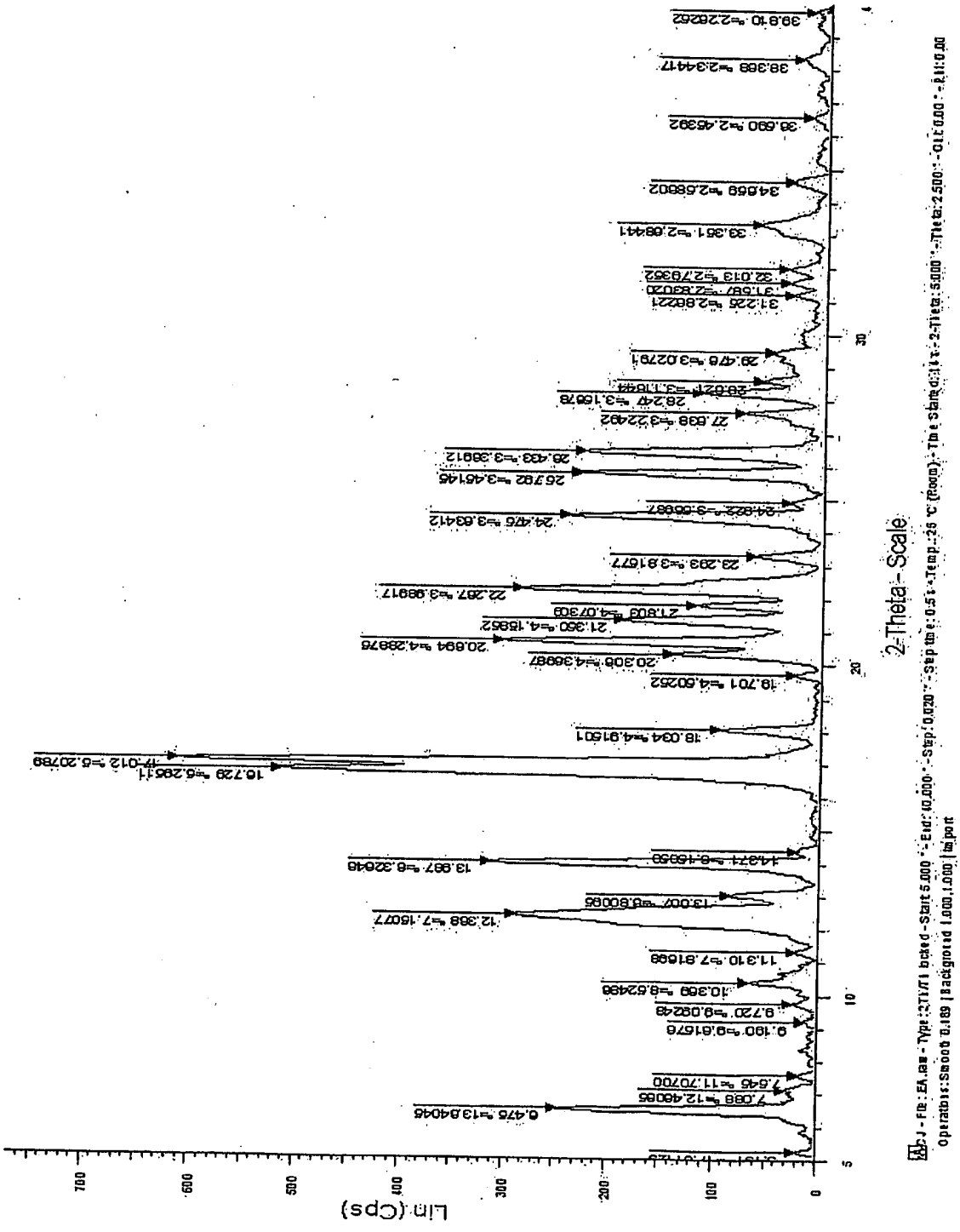
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Fig. 3

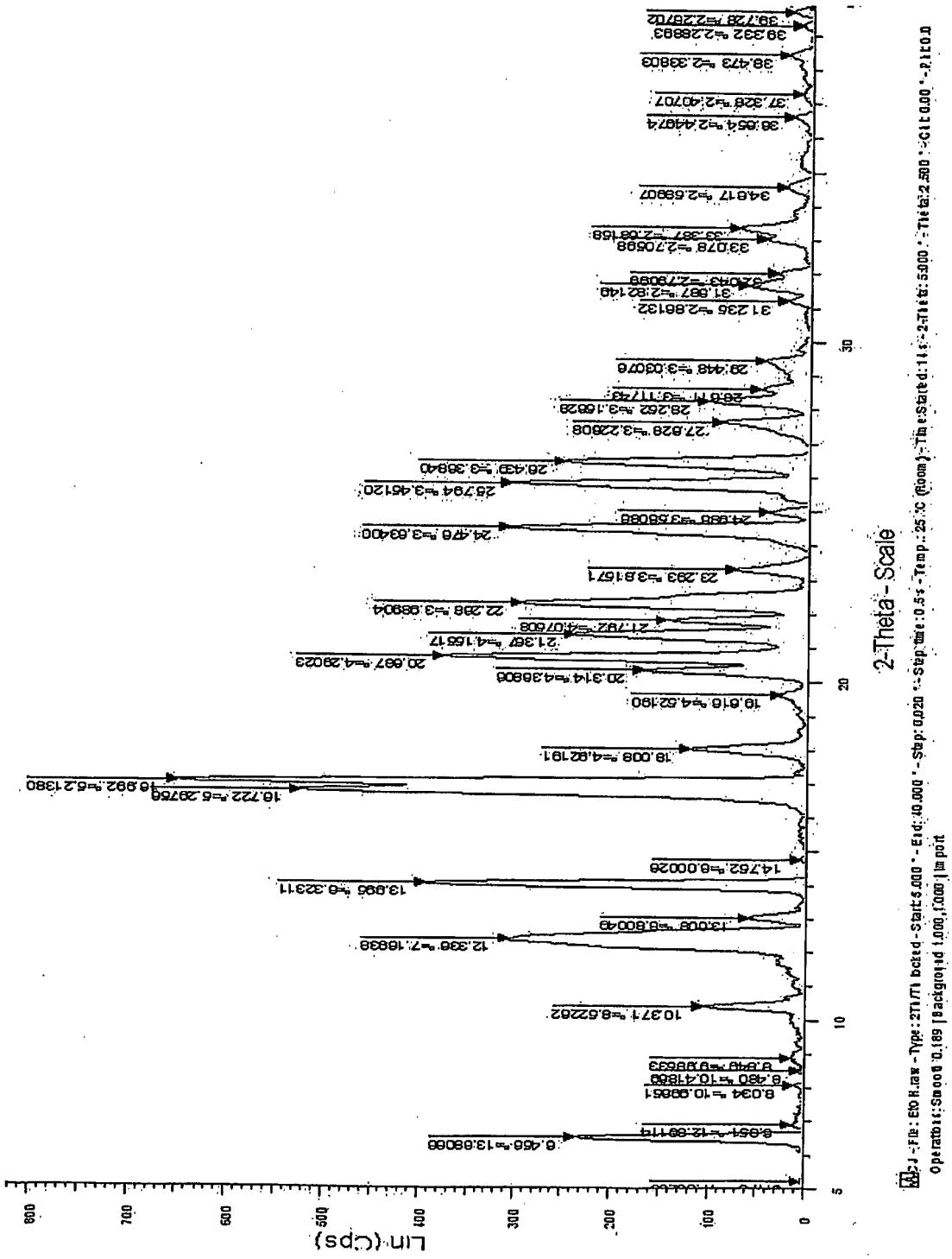
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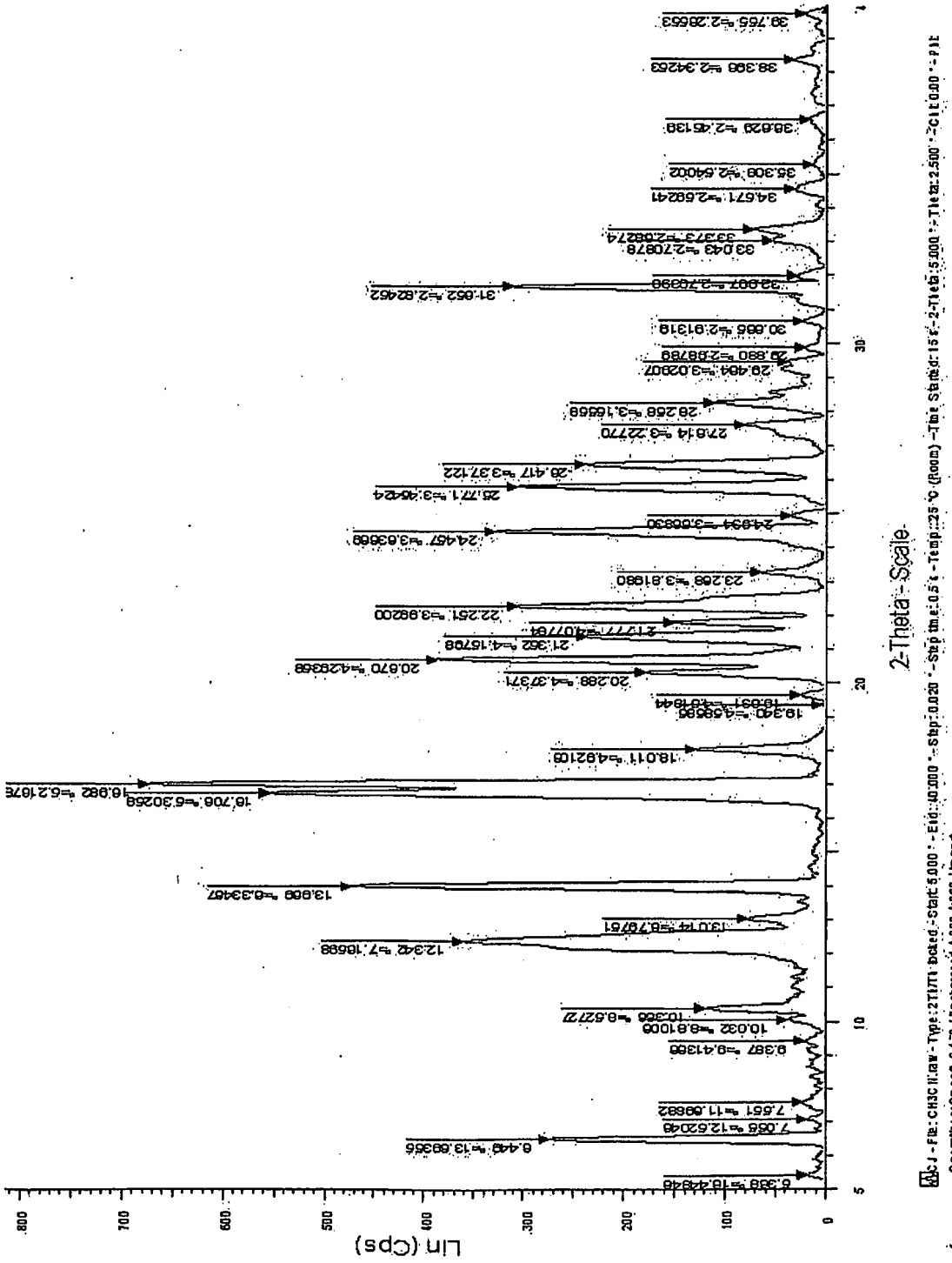
Fig. 4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2-Theta- Scale
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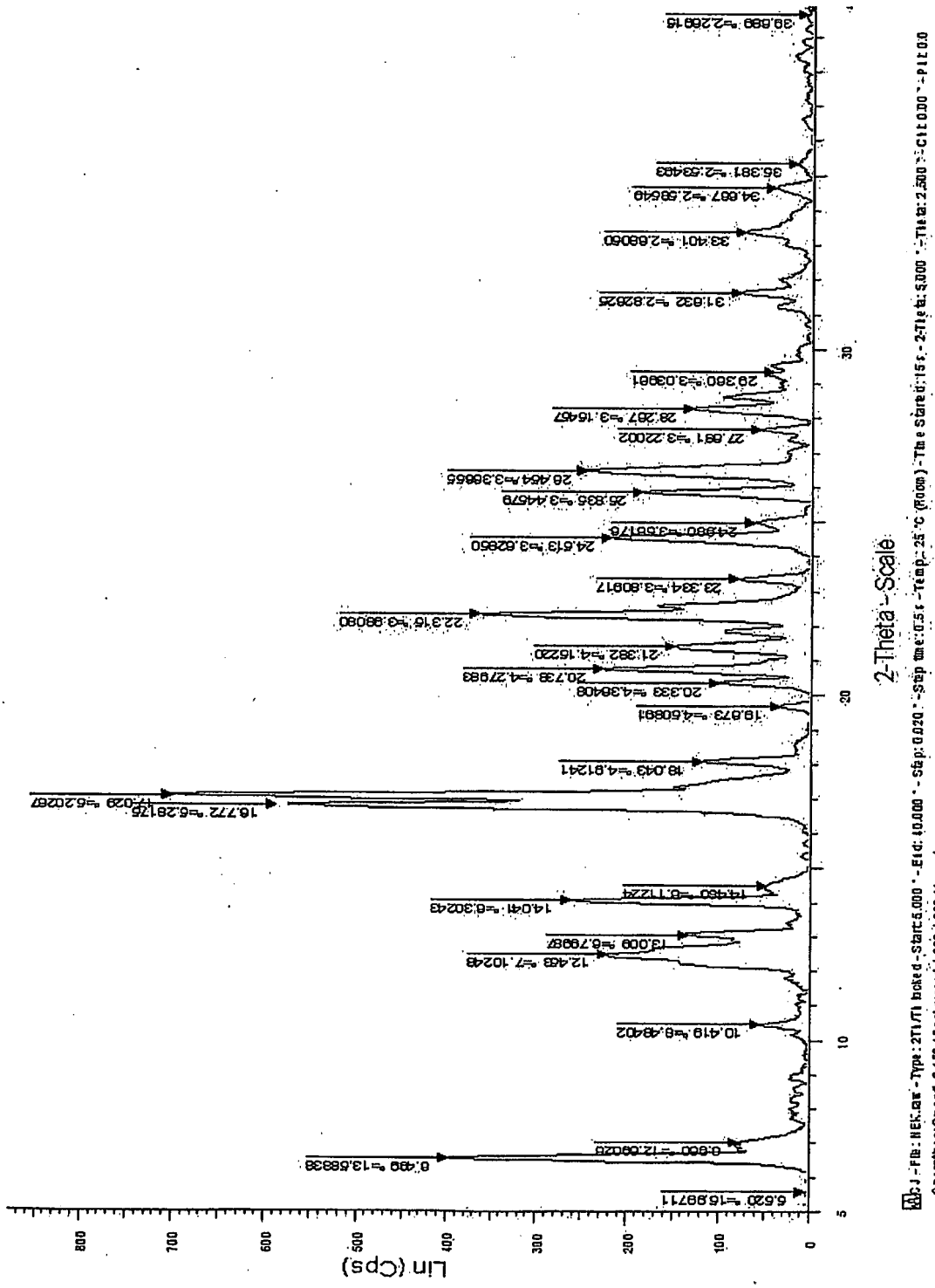
3/5

Fig. 5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27.081 =3.29202
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Fig. 6

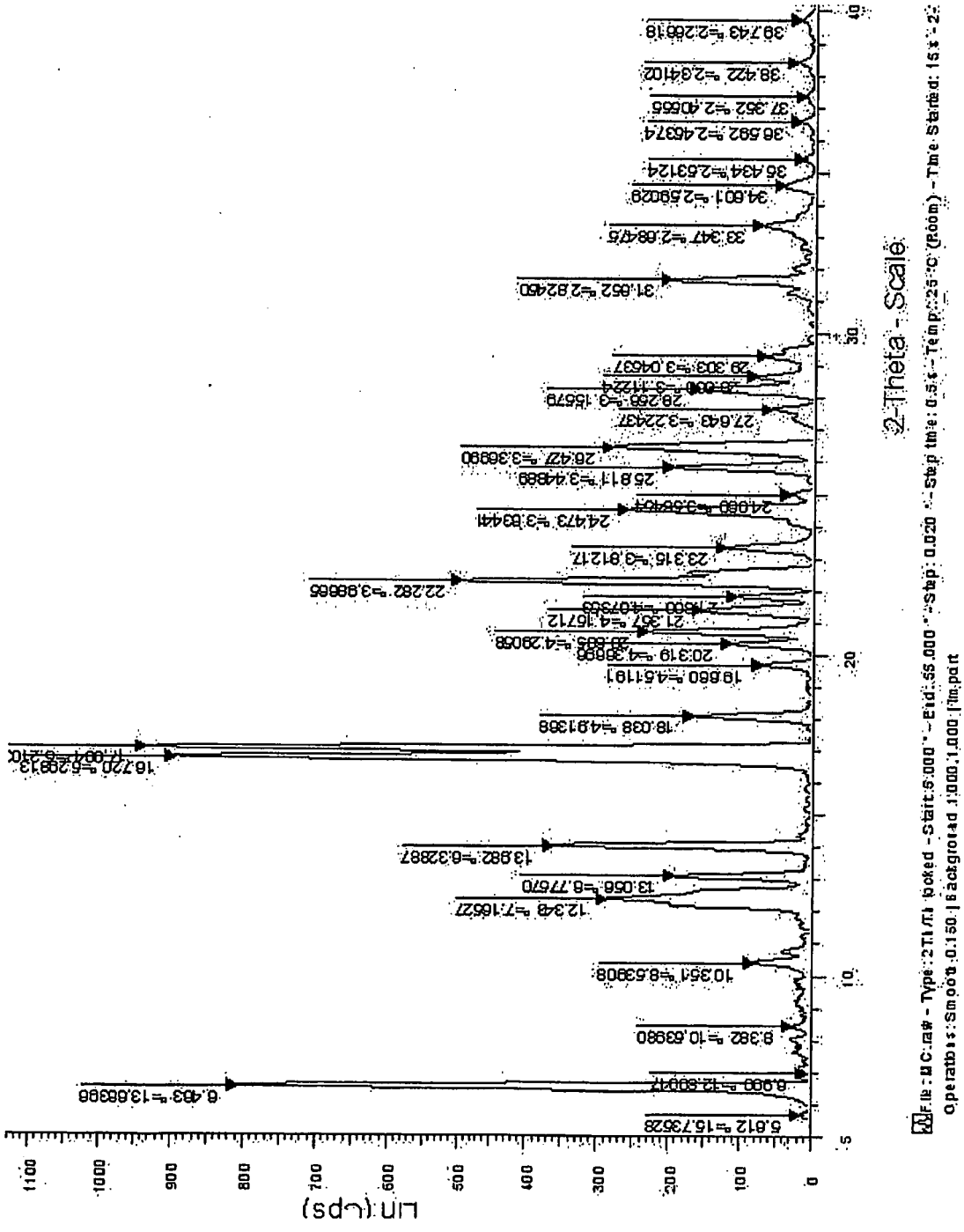
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Fig. 7

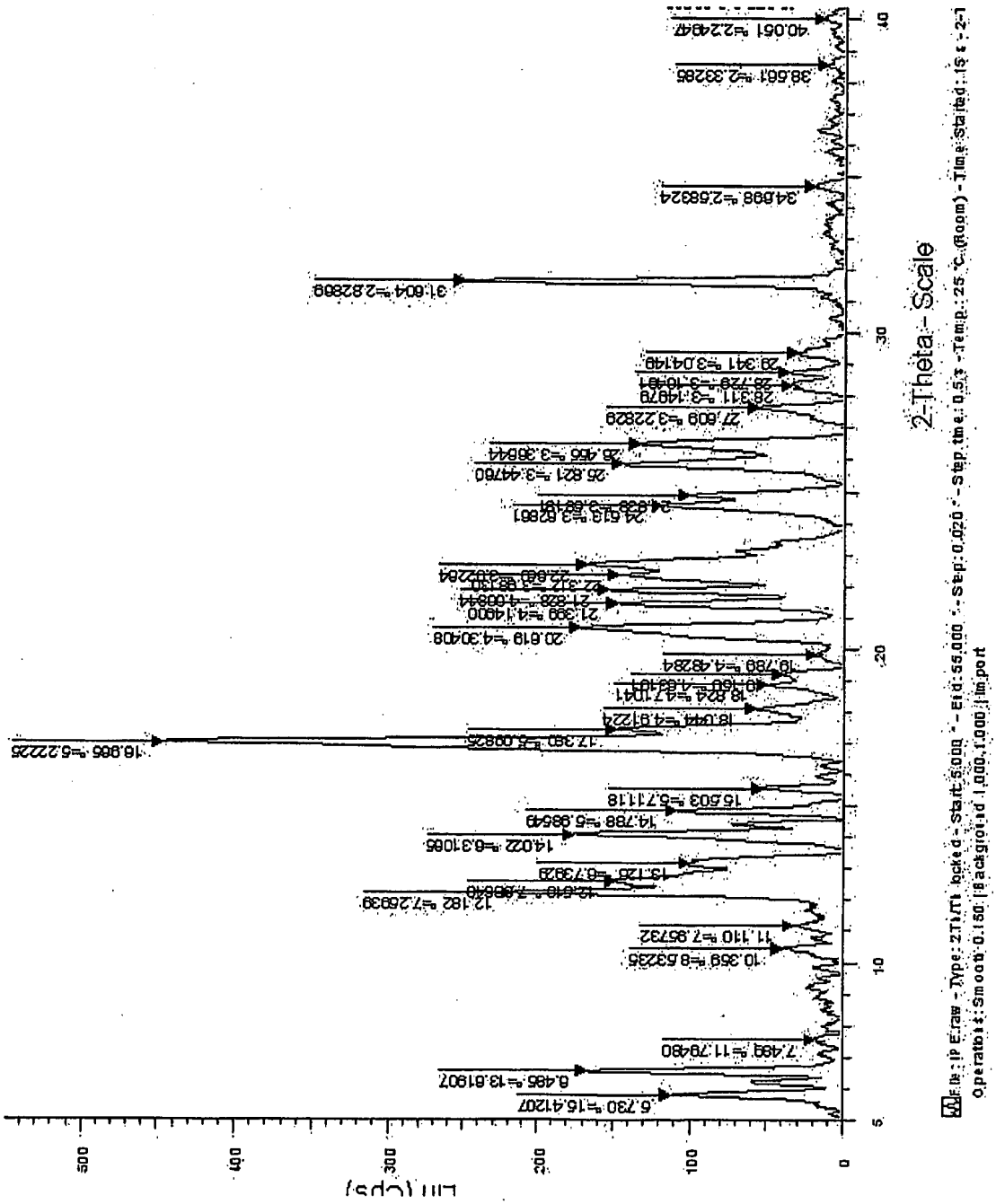
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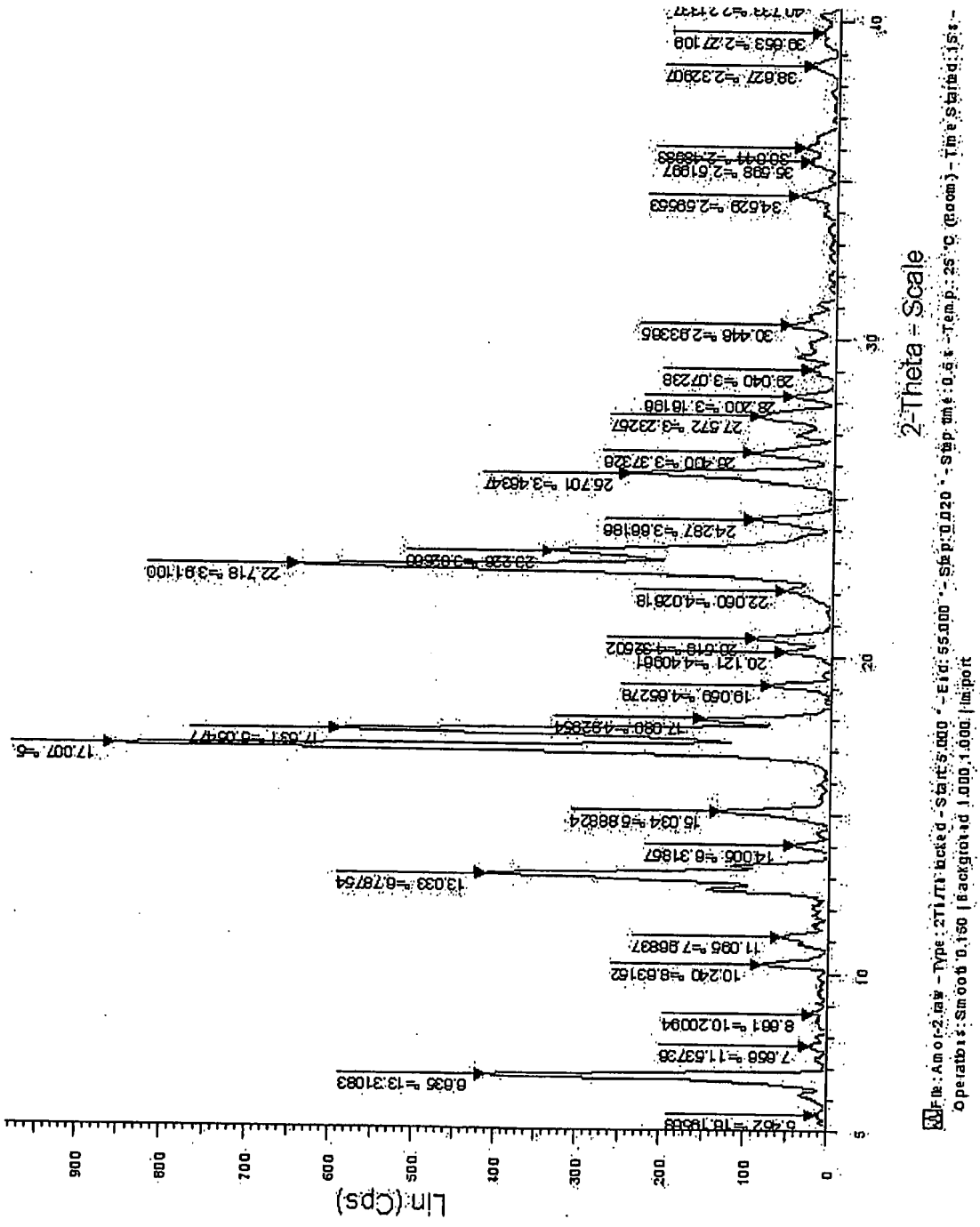
Fig. 8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14.005 = 6.318577
15.034 = 5.888824
17.007 = 5.
17.080 = 4.928524
17.651 = 5.057477
19.069 = 4.652782
20.121 = 4.409061
20.618 = 4.302602
22.060 = 4.026818
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26.400 = 3.373128
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28.200 = 3.161886
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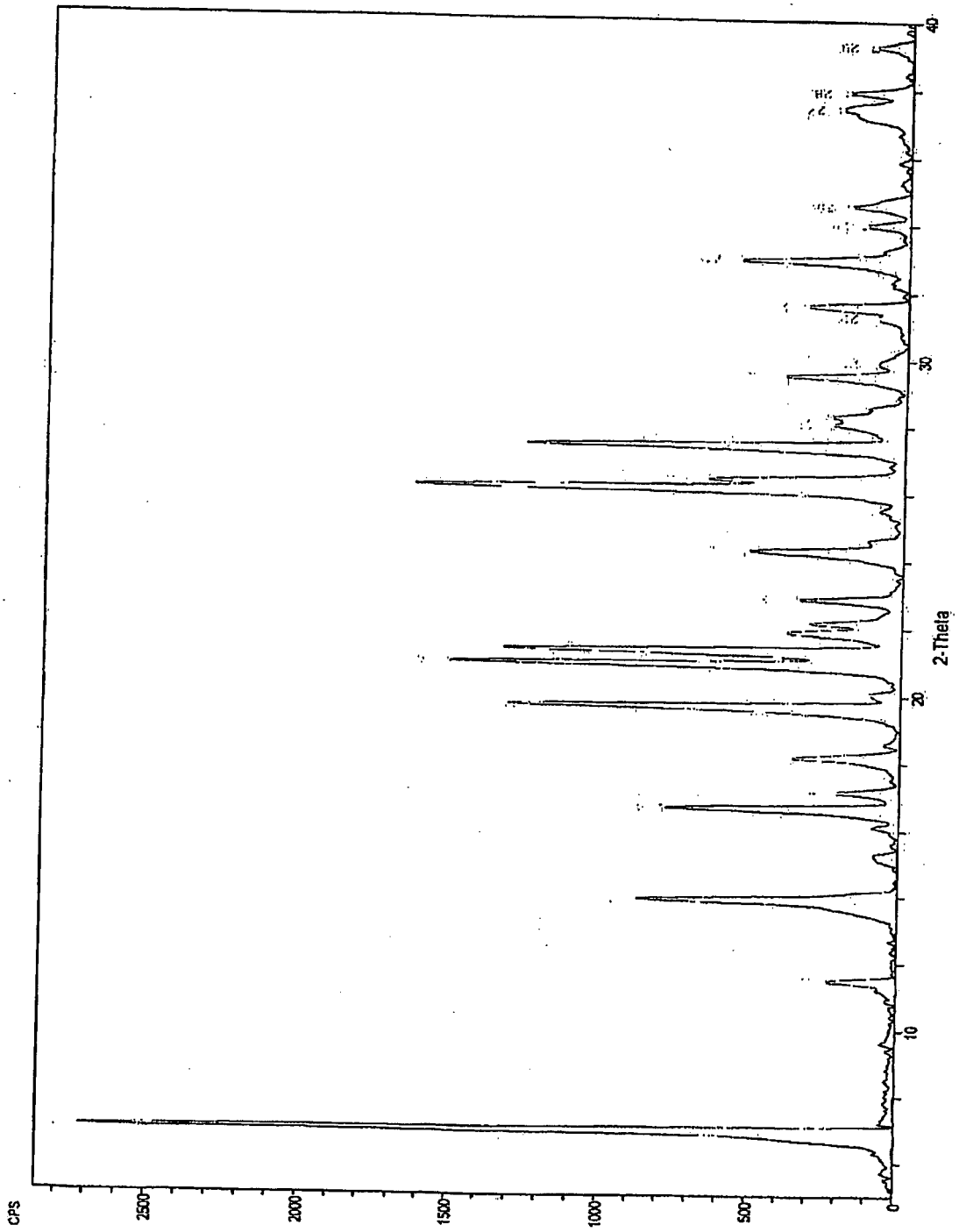
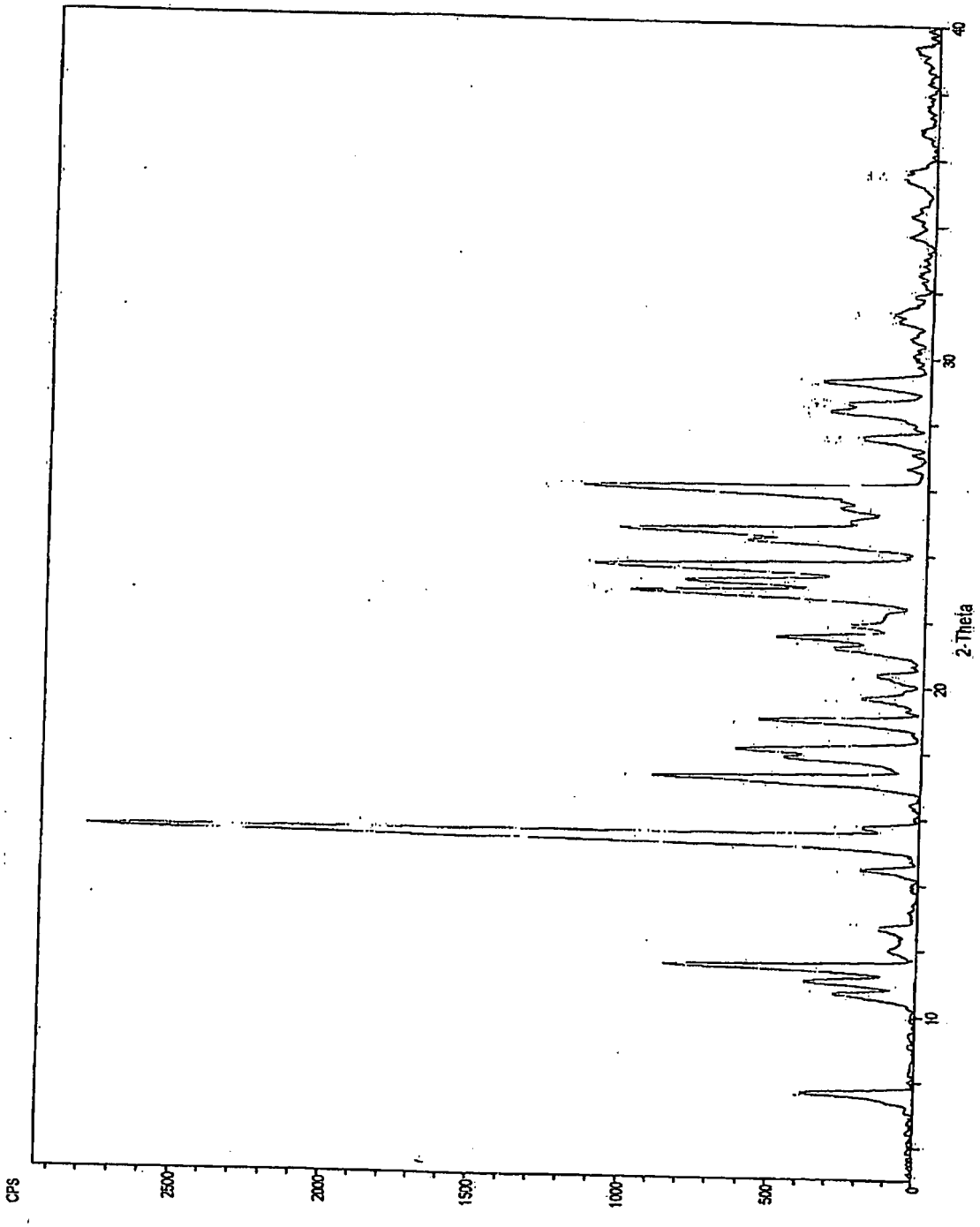
Fig. 9



5/5/1

Fig. 10



PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PCTA9512-827	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/KR2006/000073**	International filing date *(day/month/year)* **06 JANUARY 2006 (06.01.2006)**	(Earliest) Priority Date *(day/month/year)* 06 JANUARY 2005 (06.01.2005)
Applicant **CJ Corporation et al**		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      ☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ because the applicant failed to suggest a figure.
      ☐ because this figure better characterizes the invention.
   b. ☒ none of the figure is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2006/000073

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claim 13 do not required an international preliminary examination with respect to industrial applicability as it is a method of treating or preventing obesity and related disorders, depression, Parkinson's disease and so on.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2006/000073

A. CLASSIFICATION OF SUBJECT MATTER

C07C 211/29(2006.01)i, A61K 31/135(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 8 C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and Applications for Inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
CAS on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/13034 A1 (KNOLL AG , KELLY PETER FINIAN , JONES STEPHEN PAUL) 2 April 1998 see the whole documents	1-12
A	US 6,331,571 B1 (Sepracor, Inc) 18 December 2001 see the whole documents	1-12
A	WO 95/21615 A1(THE BOOTS COMPANY PLC BUCKETT, William, Roger) 17 August 1995 see the whole documents	1-12
A	WO 00/56313 A1(KNOLL PHARMACEUTICAL COMPANY) 28 September 2000 see the whole documents	1-12
A	WO 00/56310 A1(KNOLL PHARMACEUTICAL COMPANY) 28 September 2000 see the whole documents	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 APRIL 2006 (13.04.2006)	**14 APRIL 2006 (14.04.2006)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea	LEE, Suk Ju
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-8149

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2006/000073

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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